The Fat Lady Sings Again

Vanfleteren, Lowie E. G. W.; Slebos, Dirk-Jan

Published in:
Respiration

DOI:
10.1159/000481574

Editorial Comment

Respiration

Respiration 2017;94:488–490
DOI: 10.1159/000481574

Received: September 17, 2017
Accepted: September 17, 2017
Published online: October 19, 2017

The Fat Lady Sings Again

Lowie E.G.W. Vanfleteren[a, b] Dirk-Jan Slebos[c]

[a]Department of Development and Education, CIRO+, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands; [b]Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands; [c]Department of Pulmonary Diseases, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

In 1968, Filley et al. [1] made the historical description of the *pink puffer* (emphysematous type with a "cachectic" impression) and the *blue bloater* (chronic bronchitis type with a "metabolic" impression). Hence, for almost 50 years of literature, the importance of body composition in clinical phenotyping of airways disease has been recognized. In 1989, Wilson et al. [2] described that a low body weight was related to worse airflow obstruction, worse exercise capacity, more hyperinflation, worse diffusion capacity, and excess mortality. Ever since then, there was substantial and growing interest in nutrition as a determinant of the course and prognosis in chronic obstructive pulmonary disease (COPD). As it was commonly observed in advanced COPD, in previous years, it was believed that accelerated weight loss was a unifying concept in patients with COPD.

It is now clear that low body weight and ongoing weight loss is only present in a proportion of patients with COPD. Interestingly, distinct clusters and/or phenotypes of patients with COPD can be identified, in which differences in body weight and body composition are defining characteristics [3]. In fact, in COPD, obesity is more prevalent compared to underweight [3]. The presence and impact of obesity and metabolic syndrome in subjects with COPD have been recognized [4].

Countless studies have documented the importance of abdominal obesity and visceral adipose tissue in the development of cardiometabolic disease which has led to the introduction of waist circumference as a defining feature of the metabolic syndrome. With cardiovascular disease as the major comorbidity in COPD, together with the increased recognition of obesity in COPD, and the contribution of fat tissue to low-grade systemic inflammation, a role for fat tissue was seen as a link between COPD and its comorbidities. Indeed, it has been postulated that the lungs, bone marrow, and adipose tissue form a network, interconnected by vasculature and with significant implications for the pathobiology of COPD and, potentially, other chronic noncommunicable diseases that frequently coexist with COPD [5].

A further interest was seen in recent years in the role of the visceral fat compartment in COPD. Increased visceral fat (independent of total fat mass) was found in subjects with COPD compared to matched cohorts [6, 7]. Furthermore, a contribution of visceral fat to inflammatory pathways was demonstrated in older persons with obstructive lung disease and was associated with increased mortality [6]. COPD patients had increased metabolic activity as measured by FDG uptake of the abdominal visceral fat compared to non-COPD subjects. In ad-

E-Mail karger@karger.com
www.karger.com/res

Dirk-Jan Slebos
Department of Pulmonary Diseases
University Medical Center Groningen, University of Groningen
PO Box 30001, NL–9700 RB Groningen (The Netherlands)
E-Mail d.j.slebos@umcg.nl

dition, the degree of FDG uptake in the visceral and subcutaneous fat independently predicted the inflammation of the aortic wall [8].

Despite remarkable recent progress in our understanding of the complex biology of fat tissue and its relationship to lung health and disease, the pathophysiological interactions between different sources of fat tissue and the development of different pulmonary phenotypes are less studied.

In this issue of *Respiration*, Grace et al. [9] report the results of their study of thoracic adipose tissue depots evaluated using chest computed tomography (CT) scans at baseline and after 6 years in 68 current and former smokers. They found that the presence of subcutaneous but not mediastinal chest fat was associated with less emphysema progression over time in smokers. In contrast, they found that mediastinal fat was associated with a lower walking distance and less impairment in walking distance over time. This single-center observational study with a small number of subjects and with only one point of follow-up measurement after 6 years needs confirmation and elaboration. In this study it is not possible to address causality as also the potential effect of emphysema progression on loss of fat tissue needs to be considered. Interestingly, lung volume reduction surgery in patients with severe emphysema resulted in an increase in both body weight and fat-free mass 6 months after surgery [10], implying a role of disease-specific features on body composition.

However, it is intriguing to speculate that the amount of subcutaneous fat has a potential protective effect against emphysema progression. Interestingly, previous literature corroboratively suggested a role for body composition and fat tissue in the pathophysiology of emphysema and/or airway disease, which may also further relate to a lung–adipose tissue physiology interaction as postulated here above. A cross-sectional study showed that independent of airflow obstruction, age, and smoking history, obesity was negatively associated with the presence of emphysema, defined as percentage of low attenuation areas below –950 Houndfield units [11]. A Japanese study showed that epicardial fat accumulation was independently associated with the airway wall thickness in COPD patients, but not with low attenuation areas on CT [12]. Many studies have suggested that malnutrition and starvation may contribute to the development of emphysema. In a rat model, induced starvation was associated with aggravated elastase-induced injury, which was reversed with refeeding [13, 14]. Autopsies undertaken on starved patients during World War II revealed signs of emphysema in relatively young individuals [15]. In addition, early levels of emphysema have been detected after chronic malnutrition, such as in patients with anorexia nervosa [16]. Together these data suggest that more pronounced fat deposition may potentially protect against the development of emphysema. From this point of view it is of interest to evaluate what is known on pathophysiological interactions of proteins produced by adipose tissue, so-called adipokines and development of emphysema. Dysregulation of adipokines plays a crucial role in a variety of metabolic processes, such as obesity. Two key adipokines, leptin and adiponectin, are produced mainly by adipocytes and have broadly opposing functions [17]. In health, leptin acts centrally to induce satiety; however, because of leptin resistance, most obese subjects have high leptin levels. Adiponectin is the most abundant adipokine and is involved in a wide variety of physiological processes. Serum levels of adiponectin decrease with obesity and are positively associated with insulin sensitivity [18]. Because of their regulatory role in immune responses and their increased expression by bronchial epithelial cells and alveolar macrophages, their potential role in COPD-related pathophysiology has been put forward [19]. Higher plasma adiponectin levels have been repeatedly shown associated with CT-assessed emphysema [20, 21]. Then again, plasma leptin and the leptin/adiponectin ratio, but not adiponectin, were significantly associated with changes in CT-assessed emphysema, suggesting a potential role as a biomarker in emphysema progression [21]. These data suggest a possible contribution of adipokines in the development of emphysema. Although data need further in-depth exploration, these findings are intriguing as adiponectin-deficient mice seem protected against tobacco-induced inflammation and emphysema [22].

In order to increase our understanding of the pathophysiology of COPD and emphysema, we believe it is of utmost importance to study interactions of different organ systems, including in-depth evaluation of the biological interactions of fat and lung tissue. The study by Grace et al. [9] suggests that different fat compartmentation differentially impacts on COPD-related disease outcomes and potentially progression. Given that chest CT is commonly done in COPD-related research, it is emphasized to include these measurements of fat compartments as study variables. In addition, not only the anatomical presence and location of fat tissue but also in-depth evaluation of the endocrine and immunological function of fat tissue in relation to COPD phenotype-specific pathophysiology need further exploration.

References

1 Filley GF, et al: Chronic obstructive bronchopulmonary disease. II. Oxygen transport in two clinical types. Am J Med 1968;44:26–38.
2 Wilson DO, et al: Body weight in chronic obstructive pulmonary disease. The National Institutes of Health Intermittent Positive-Pressure Breathing Trial. Am Rev Respir Dis 1989; 139:1435–1438.
3 Vanfleteren LE, et al: Clusters of comorbidities based on validated objective measurements and systemic inflammation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;187:728–735.
4 Breyer MK, et al: Prevalence of metabolic syndrome in COPD patients and its consequences. PLoS One 2014;9:e98013.
5 Agusti A, et al: Lungs, bone marrow, and adipose tissue. A network approach to the pathobiology of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;188: 1396–1406.
6 van den Borst B, et al: The influence of abdominal visceral fat on inflammatory pathways and mortality risk in obstructive lung disease. Am J Clin Nutr 2012;96:516–526.
7 Furutate R, et al: Excessive visceral fat accumulation in advanced chronic obstructive pulmonary disease. Int J Chron Obstruct Pulmon Dis 2011;6:423–430.
8 Vanfleteren LE, et al: A possible link between increased metabolic activity of fat tissue and aortic wall inflammation in subjects with COPD. A retrospective F-FDG-PET/CT pilot study. Respir Med 2014;108:883–890.
9 Grace J, et al: Mediastinal and subcutaneous chest fat are differentially associated with emphysema progression and clinical outcomes in smokers. Respiration 2017, DOI: 10.1159/000479886.
10 Nezu K, et al: The change in body composition after bilateral lung volume reduction surgery for underweight patients with severe emphysema. Lung 2000;178:381–389.
11 Gu S, et al: Obesity and extent of emphysema depicted at CT. Clin Radiol 2015;70:e14–e19.
12 Higami Y, et al: Increased epicardial adipose tissue is associated with the airway dominant phenotype of chronic obstructive pulmonary disease. PLoS One 2016;11:e0148794.
13 Sahebjami H, Domino M: Effects of starvation and refeeding on elastase-induced emphysema. J Appl Physiol (1985) 1989;66: 2611–2616.
14 Sahebjami H, MacGee J: Changes in connective tissue composition of the lung in starvation and refeeding. Am Rev Respir Dis 1983; 128:644–647.
15 Fliederbaum J: Clinical aspects of hunger disease in adults; in Winick M (ed): Hunger Disease: Studies by the Jewish Physicians in the Warsaw Ghetto. New York, John Wiley & Sons, 1979, pp 11–36.
16 Coxson HO, et al: Early emphysema in patients with anorexia nervosa. Am J Respir Crit Care Med 2004;170:748–752.
17 Ouchi N, et al: Adipokines in inflammation and metabolic disease. Nat Rev Immunol 2011;11:85–97.
18 Hotta K, et al: Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595–1599.
19 Vernooy JH, et al: Enhanced pulmonary leptin expression in patients with severe COPD and asymptomatic smokers. Thorax 2009;64:26–32.
20 Carolan BJ, et al: The association of adiponectin with computed tomography phenotypes in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2013;188:561–566.
21 Oh YM, et al: Association of plasma adipokines with chronic obstructive pulmonary disease severity and progression. Ann Am Thorac Soc 2015;12:1005–1012.
22 Miller M, et al: Adiponectin-deficient mice are protected against tobacco-induced inflammation and increased emphysema. Am J Physiol Lung Cell Mol Physiol 2010;299: L834–L842.